

## REMARKS

Claims 40-59 are pending in this application. Claims 40-55 are withdrawn. Claim 58 is canceled. New claims 60-63 are added. Favorable reconsideration of this application is respectfully requested in view of the amendments above and remarks below.

### **I. Restriction/Election**

Applicants traverse this Restriction/Election requirement on the grounds that reviewing the pending claims will not be a burden on the Examiner. However, in order to provide a complete response, Applicants elect to prosecute Group 2, claims 56-59 and the species of JP-like subtilase modified by an amino acid substitution at a position corresponding to S193 in SEQ ID NO: 1 (Claims 56-57, 59-63 read thereon).

### **II: Objections to the Specification**

The Examiner has objected to the specification because Figures 1 and 4 contain amino acid sequences, which are not identified by a SEQ ID NO. Also Table in Appendix 1 is required to have a SEQ ID NO. Moreover, the Examiner has stated that each time that reference is made to the JP170 subtilase in the specification, or the amino acid sequence of another, specific, subtilase e.g. at pages 3-5, 8-11, 15, 18-20 (with respect to the positions enumerated), and 22, or in the claims, it should be accompanied by the sequence identifier, e.g., SEQ ID NO: 1.

Applicants respectfully submit that the requested changes are numerous and will be difficult to process by the USPTO. In order to minimize the burden of processing such changes, Applicants voluntarily submit a substitute specification pursuant to 37 CFR 1.25(b) making the many changes suggested by the Examiner. For example, the specification has been amended, *inter alia*, to amend the Figure descriptions and description of Appendix 1 so that they include the appropriate SEQ ID NOS. Thus, the Figures and Appendix have the requisite SEQ ID NO. Moreover, references to JP170 subtilase have been changed in the specification where the terms may refer to SEQ ID NO.:1.

Pursuant to 37 CFR 1.25(c) a substitute specification is submitted with markings showing all the changes relative to the immediate prior version of the specification of record. Further an accompanying clean version (without markings) is also supplied.

Pursuant to 37 CFR 1.25(b) the substitute specification contains no new matter.

Applicants at this time would like to modify the specification by specifically adding SEQ ID No: 8. As Fig. 4 showed the three-dimensional alignment of various subtilases including Savinase (No. 3 in Fig. 4), no new matter is being added.

Applicants enclose a computer-readable form of the Sequence Listing. The computer-readable form and the paper sequence listing included herewith are the same.

Replacement of the old specification with the substitute specification attached hereto is requested. Further, entry of the sequence listing included herewith is requested.

### **III: Objections to the Claims**

Claim 57 was objected to because the transition between the claims preamble and each of the clauses (a) - (c) are allegedly misleading and clauses (b) -(c) are in part redundant. Claim 57 is amended herein and thus the objection is moot. Reconsideration of claim 57, as amended, is requested.

### **IV. The Rejection of Claims 56, 57 and 59 under 35 U.S.C. 112**

Claims 56, 57 and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Applicants submit that this rejection is rendered moot by the amended claims 56 and 59. The amended claims recite a degree of sequence similarity of at least 90%. Applicants respectfully submit that the claimed subject matter is described in the specification in a manner that reasonably conveys to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, an artisan would appreciate that Applicants had possession of variants which are

highly similar to the reference sequence, SEQ ID NO:1. The specification fully describes the variants of the present disclosure. Applicants therefore submit that the specification demonstrates that Applicants had possession of the claimed invention at the time the application was filed.

For the foregoing reasons, Applicants submit that the amended claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

### **III. The Rejection of Claims 56, 57 and 59 under 35 U.S.C. 112**

Claims 56, 57 and 59 are rejected under 35 U.S.C. 112, as lacking enablement.

In order to expedite prosecution, the claims have been amended to recite a similarity of at least 90% to SEQ ID NO: 1.

Moreover, it is well settled that "[t]he first paragraph of section 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Moreover, "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 USPQ at 369.

In the present application, the specification contains a complete description of materials and methods for producing subtilase variants. See, among other places, Methods of producing subtilase variants at page 51. It is well within the skill of the art to isolate and identify the claimed variants using the Applicants' disclosure.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

**IV. The Rejection of Claims 56, 57 and 59 under 35 U.S.C. 112 (indefinite)**

Claims 56, 57 and 59 stand rejected as indefinite for various reasons. These claims are amended herein to make them clear. Reconsideration is urged.

**V. The Rejection of Claims 59 under 35 U.S.C. 103**

Claim 59 stands rejected under 35 U.S.C. 103 as allegedly obvious over U.S. Patent No. 5,891,701 (hereinafter referred to simply as "Sloma") and U.S. Patent No. 5,397,705 (hereinafter referred to simply as "Zukowski"). This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.1991).

The present disclosure relates to a variant of a JP170 type subtilase including at least one modification in an amino acid residue in a position located at a distance of 10Å or less to one or more ion-binding sites, wherein the subtilase has at least 90% similarity to SEQ ID NO: 1. Claim 59, as amended, requires that the variant has the a degree of similarity of at least 90% to SEQ ID NO:1.

Sloma relates to isolated nucleic acid sequences encoding polypeptides having protease activity, in which the polypeptides are obtainable from an alkalophilic *Bacillus* species having enhanced stability towards bleaching agents of the peroxy type. Although Sloma teaches the amino acid sequence of SEQ ID NO 1 of the Applicant's disclosure, the Examiner has correctly asserted that Sloma does not teach any particular regions within the amino acid sequence of the JP170 subtilase for the substitution of amino acid.

Moreover, the Examiner has correctly asserted that Sloma does not teach the locations of any ion binding sites of the JP170 subtilase.

Zukowski fails to cure the deficiencies of Sloma. In particular, nowhere does Zukowski describe a variant of JP170 type subtilase including at least one modification in the claimed binding site positions, wherein the subtilase has at least 90% similarity to SEQ ID NO:1. Thus, nowhere do Sloma or Zukowski teach or suggest a variant of JP170 type subtilase including at least one modification in at least one position recited in claim 59, wherein the subtilase has at least 90% similarity to SEQ ID NO:1.

Applicants note that during the determination of the crystal structure of the JP170 subtilase in accordance with the present disclosure, it was found that the claimed variant did not contain the ion-binding sites corresponding to the ion-binding sites in the BPN' subtilase. More specifically, Applicants direct the Examiners attention to the Applicants' specification at page 16, lines 11-16. Here, Applicants disclosure provides:

The JP170 subtilases were found to lack the well-known Strong and Weak ion-binding sites of the BPN' subtilases. However, the JP170 subtilases have three ion-binding sites which are not present in the BPN' subtilisin structures. This can be seen in the structural alignment presented in Fig. 2. These three ion-binding sites are hereinafter referred to as Site 1, which is placed in the catalytic domain, and Site 2 and 3 which are placed in the non-catalytic C-terminal domain.

Consequently, If one of skill in the art were to combine the teachings of Sloma and Zukowski (which Applicants do not concede is proper) the result would simply be to use the sequence of Sloma with the calcium binding sites of Zukowski. Thus, one is just as likely to arrive at a combination of Sloma and Zukowski having modifications at positions other than those specifically required by claim 59. Accordingly, nothing in any reference would teach suggest or motivate one skilled in the art to make modifications to a variant of JP170 type subtilase wherein the subtilase has at least 90% similarity to SEQ ID NO:1.

The only motivation offered by the Examiner to combine Sloma and Zukowski is that Sloma teaches that amino acid substitutions should be made in the JP170 subtilase for a set of reasons amino acid substitutions have been made in other subtilases. Applicants

respectfully traverse the Examiner's position and submit that this is improper for the following reasons.

First, Applicants submit that the claimed invention is novel, *i.e.* not suggested in the prior art (*e.g.*: there are no remaining rejections under 35 U.S.C. 102). Where the prior art suggests that an area should be investigated, and yet the resulting invention is not suggested in the prior art, the claimed invention is not obvious. See for example, *In re Eli Lilly*, 902 F.2d, 943,945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990) ("An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.) The fact that Sloma says that it may be of interest to synthesize variants of the polypeptide where the variants differ in specific activity, thermostability, oxidative stability, pH optimum or the like using, for example site-directed mutagenesis is not instructive on what changes could specifically be made, and does not provide motivation for one to combine this reference with Zukowski. The use of the word "may" by Sloma suggests that Sloma is limited to merely suggesting an area be investigated. Accordingly, the Examiner is using improper obvious to try rational and independent claim 59 is not obvious.

Even assuming that the Examiner is correct in that methods of Sloma could be used with the methods of Zukowski (which Applicants do not concede would be proper), the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir.1990). See also, *In re Jones*, where the Court found there was no suggestion to combine the references to arrive at the claimed invention. Note, as the prior art does not even teach how to identify and modify the residues involved in calcium binding in accordance with the claimed invention, thus the prior art could not suggest the desirability of an unknown combination. Accordingly, independent claim 59 is not obvious and reconsideration is urged.



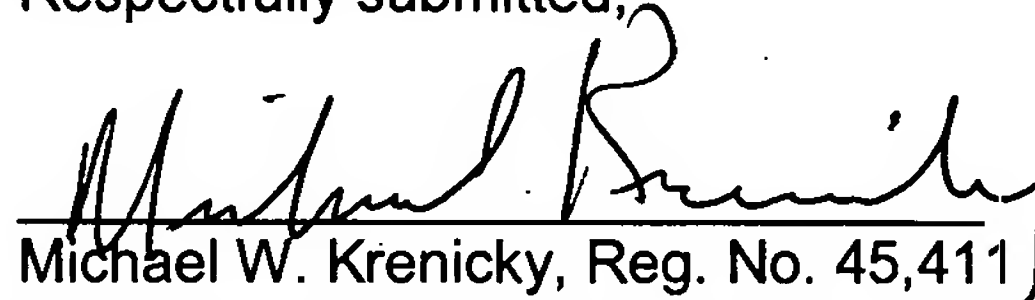
For the foregoing reasons, Applicants submit that the claim 59 is not obvious and the amendments and remarks herein overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

**VI. Conclusion**

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

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Respectfully submitted,



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